IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	)	Examiner: O'Hara, Eileen B.
Avi J. ASHKENAZI, et al.	)	Art Unit: 1646
Application Serial No. 09/978,192	)	Confirmation No: 3437
Filed: October 15, 2001	)	Attorney's Docket No. GNE-2630 P1C9
For: **SECRETED AND TRANSMEMBRANE POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THE SAME**	)	**Customer No. 77845**

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RESPONSE TO NOTICE OF NON-COMPLIANT APPEAL BRIEF

MAIL STOP APPEAL BRIEF - PATENTS
Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

On November 1, 2006, the Examiner made a final rejection to pending Claims 58-62. A Response to Final Office Action was filed on February 1, 2007. An Advisory Action was mailed on March 1, 2007. A Notice of Appeal was subsequently filed on April 2, 2007 and an Appeal Brief was filed on November 2, 2007.

A Notification of Non-Compliant Appeal Brief was mailed February 11, 2008, which stated that the Appeal Brief did not fit with the criteria of 37 C.F.R. §41.37(c)(1)(viii)). The following amended Appeal Brief has been corrected with regards to the claim language of Claims 60 and 61 in the Claims Appendix, as requested by the Examiner.

To reduce expense and duplication, Appellants hereby resubmit their Appeal Brief without the previously disclosed materials in the evidence appendix. The Board is requested to refer to the Evidence Appendix submitted with the Appeal Brief dated November 2, 2007.

The following constitutes the amended version of Appellants' Brief on Appeal.

1. REAL PARTY IN INTEREST

The real party in interest is Genentech, Inc., South San Francisco, California, by an assignment of the parent application U.S. Patent Application Serial No. 09/918,585 recorded October 24, 2001, at Reel 012095 and Frame 0677.

2. RELATED APPEALS AND INTERFERENCES

The claims pending in the current application are directed to antibodies to a polypeptide referred to herein as "PRO274." There exists one related pending patent application, U.S. Patent Application Serial No. 09/978,188, filed October 15, 2001 (containing claims directed to PRO274 polypeptides). This related application is also under final rejection from the same Examiner and based upon very similar reasons, wherein appeal of these final rejections are being pursued independently and concurrently herewith. Although there exist several applications directed to the "gene amplification" utility, in general, under Appeal, none of these are related to PRO274 molecules or antibodies binding to it.

3. STATUS OF CLAIMS

Claims 58-62 are in this application.

Claims 1-57 and 63 are canceled.

Claims 58-62 stand rejected and Appellants appeal the rejection of these claims.

A copy of the rejected claims in the present Appeal is provided as Appendix A.

4. STATUS OF AMENDMENTS

All prior amendments have been entered by the Examiner. No claim amendments have been submitted after the Response filed August 3, 2006.

5. SUMMARY OF THE INVENTION

The invention claimed in the present application concerns an isolated antibody that specifically binds to the polypeptide of SEQ ID NO:7 (Claim 58). The invention further provides monoclonal antibodies (Claim 59), humanized antibodies (Claim 60), antibody fragments (Claim 61), and labeled antibodies (Claim 62) that specifically bind to the polypeptide of SEQ ID NO:7.

Support for the preparation and uses of antibodies is found throughout the specification, including, for example, pages 217-225. The preparation of antibodies is described in Example 104, while Example 106 describes the use of the antibodies for purifying the polypeptides to which they bind. Isolated antibodies are defined in the specification at page 132, lines 29-38. Support for monoclonal antibodies is found in the specification at, for example, page 217, line 30, to page 219, line 11, and Example 104. Support for humanized antibodies is found in the specification at, for example, page 219, line 12, to page 220, line 14. Support for antibody fragments is found in the specification at, for example, page 131, line 29, to page 132, line 22, and page 221, lines 6-34. Support for labeled antibodies is found in the specification at, for example, page 133, lines 1-4, and page 224, line 35, to page 225, line 4.

The polypeptide of SEQ ID NO:7 is designated PRO274, and its amino acid sequence is shown in Figure 4, while the encoding nucleic acid sequence (SEQ ID NO:6) is shown in Figure 3. The specification discloses that various portions of the PRO274 polypeptide possess significant sequence similarity to the seven transmembrane receptor proteins (see, for example, page 2, line 27 to page 3, line 6). The isolation of cDNA clones encoding PRO274 of SEQ ID NO:7 is described in Example 4. Examples 100-103 describe the expression of PRO polypeptides in various host cells, including *E. coli*, mammalian cells, yeast and Baculovirus-infected insect cells. Finally, Example 114, in the specification at page 331, line 23, to page 346, line 4, sets forth a Gene Amplification assay which shows that the PRO274 gene is amplified in the genome of certain human lung and colon cancers (see page Table 9).

The specification discloses that antibodies to PRO polypeptides may be used, for example, in purification of PRO (page 225, lines 5-11 and Example 106), in diagnostic assays for PRO expression (page 190, lines 3-9, and page 224, line 21 to page 225, line 4), as antagonists to PRO (page 198, lines 3-6), and as elements of pharmaceutical compositions for the treatment of various disorders (page 223, line 30, to page 224, line 28).

6. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

I. Whether Claims 58-62 satisfy the utility requirement of 35 U.S.C. §101.

II. Whether Claims 58-62 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

III. Whether Claims 58-62 are patentable under 35 U.S.C. §102(b) over Ho *et al.*, Science, Vol. 289, pp 265-270.

IV. Whether Claims 59-62 are patentable under 35 U.S.C. §103(a) over Ho *et al.*, in view of Janeway *et al.*

7. ARGUMENT

A. Summary of the Arguments:

Issue I: Utility

Appellants rely upon the gene amplification data of the PRO274 gene for patentable utility of the PRO274 polypeptide and the antibodies that bind it. This data is clearly disclosed in the instant specification in Example 114, which discloses that the gene encoding PRO274 showed significant amplification in primary lung tumors. Appellants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung cancer or for individuals at risk for developing lung cancer.

The Examiner has asserted that it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that antibodies would be useful diagnostically. In support of these assertions, the Examiner referred to articles by Pennica *et al.* and Li *et al.* as evidence showing a lack of correlation between gene (DNA) amplification and mRNA levels, as well as articles by Gygi *et al.*, Hu *et al.*, Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.* as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels.

Appellants submit that the teachings of the Examiner's cited references do not conclusively establish a *prima facie* case for lack of utility (as will be discussed in detail below). As further support for their utility claim, Appellants have submitted a Declaration by Dr. Audrey Goddard, which explains that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for

the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2-fold to 3.1-fold amplification of PRO274 in three primary lung tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein. The Examiner has not provided any evidence to show that the disclosed DNA amplification is not significant.

Appellants have also submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. For instance, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* collectively teach that in general, gene amplification increases mRNA expression. Of note, Appellants point out that the Examiner conceded to this argument in the preceding Advisory Action.

Further, Appellants have submitted over a hundred references, along with Declarations of Dr. Paul Polakis, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels. Appellants would also like to bring to the Examiner's attention a recent decision in a microarray case by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9). Appellants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO274 polypeptide to refute Appellant's assertion of a correlation between DNA levels, mRNA levels and protein expression.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is generally a positive correlation between DNA, mRNA, and polypeptide levels, in general, in the majority of amplified genes, as exemplified by the teachings of Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* the two Polakis Declarations, the art in general overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed and has utility in the diagnosis of lung cancer.

Appellants further submit that even if there were no correlation between gene amplification and increased mRNA/protein expression, (which Appellants expressly do not concede to), a polypeptide encoded by a gene that is amplified in cancer would still have a specific, substantial, and credible utility. Appellants submit that, as evidenced by the Ashkenazi Declaration and the teachings of Hanna et al., simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy for the tumor, as demonstrated by a real-world example of the breast cancer marker HER-2/neu.

Accordingly, Appellants submit that when the proper legal standard is applied, one should reach the conclusion that the present application discloses at least one patentable utility for the claimed antibodies to PRO274 polypeptides.

Issue II: Enablement

Appellants respectfully submit that the data presented in Example 114 of the specification and the cumulative evidence of record support a "specific, substantial and credible" asserted utility for the presently claimed invention. Accordingly, one of ordinary skill in the art would understand how to make and use the recited antibodies for the diagnosis of lung cancer without any undue experimentation.

These arguments are all discussed in further detail below under the appropriate headings.

Issue III: Anticipation by Ho *et al.*

Claims 58-62 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270, published July 14, 2000.

The instant application claims priority to International Application No. PCT/US00/03565, which first disclosed the gene amplification results and was filed February 11, 2000, over five months before the publication date of Ho *et al.* The instant application has not been granted the earlier priority date on the grounds that "the gene amplification assay fails to disclose a patentable utility for the antibodies to the protein." (Page 10 of the Office Action mailed July 19, 2005). Appellants respectfully submit that as discussed above under Issues I and II, the presently claimed invention is supported by a specific, substantial and credible utility and, therefore, the present specification teaches one of ordinary

skill in the art "how to use" the claimed invention without undue experimentation. Accordingly, the instant application is entitled to the effective filing date of February 11, 2000, and thus Ho *et al.* is not prior art.

Issue IV: Obviousness over Ho *et al.* in view of Janeway *et al.*

Claims 59-62 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Immunology, The Immune System in Health and Disease, Third Edition, Janeway and Travers, Ed., 1997.

As discussed above, the instant application is entitled to priority to International Application No. PCT/US00/03565, and to the effective filing date of February 11, 2000. Thus Ho *et al.* is not prior art.

These arguments are all discussed in further detail below under the appropriate headings.

B. Detailed Arguments

Issue I: Claims 58-62 satisfy the utility requirement of 35 U.S.C. §101

The sole basis for the Examiner's rejection of Claims 58-62 under these sections is that the data presented in Example 114 of the present specification is allegedly insufficient under applicable legal standards to establish a patentable utility under 35 U.S.C. §101 for the presently claimed subject matter.

Appellants strongly disagree and respectfully traverse the rejection.

i) The Legal Standard For Utility Under 35 U.S.C. §101

According to 35 U.S.C. §101:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or composition of matter, or any new and *useful* improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
> (Emphasis added).

In interpreting the utility requirement, in *Brenner v. Manson,*[1] the Supreme Court held that the *quid pro quo* contemplated by the U.S. Constitution between the public interest and the interest of the inventors required that a patent Appellant disclose a "substantial utility" for his or

[1] *Brenner v. Manson,* 383 U.S. 519, 148 U.S.P.Q. (BNA) 689 (1966).

her invention, *i.e.*, a utility "where specific benefit exists in currently available form."[2] The Court concluded that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. A patent system must be related to the world of commerce rather than the realm of philosophy."[3]

Later, in *Nelson v. Bowler,*[4] the C.C.P.A. acknowledged that tests evidencing pharmacological activity of a compound may establish practical utility, even though they may not establish a specific therapeutic use. The Court held that "since it is crucial to provide researchers with an incentive to disclose pharmaceutical activities in as many compounds as possible, we conclude adequate proof of any such activity constitutes a showing of practical utility."[5]

In *Cross v. Iizuka,*[6] the C.A.F.C. reaffirmed *Nelson*, and added that *in vitro* results might be sufficient to support practical utility, explaining that "*in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with the particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation there between."[7] The Court perceived, "No insurmountable difficulty" in finding that, under appropriate circumstances, "*in vitro* testing, may establish a practical utility."[8]

The case law has also clearly established that Appellants' statements of utility are usually sufficient, unless such statement of utility is unbelievable on its face.[9] The PTO has the initial

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[2] *Id.* at 534, 148 U.S.P.Q. (BNA) at 695.

[3] *Id.* at 536, 148 U.S.P.Q. (BNA) at 696.

[4] *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. (BNA) 881 (C.C.P.A. 1980).

[5] *Id.* at 856, 206 U.S.P.Q. (BNA) at 883.

[6] *Cross v. Iizuka*, 753 F.2d 1047, 224 U.S.P.Q. (BNA) 739 (Fed. Cir. 1985).

[7] *Id.* at 1050, 224 U.S.P.Q. (BNA) at 747.

[8] *Id.*

[9] *In re Gazave*, 379 F.2d 973, 154 U.S.P.Q. (BNA) 92 (C.C.P.A. 1967).

burden to prove that Appellants' claims of usefulness are not believable on their face.[10] In general, an Appellant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. §101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope."[11, 12]

Compliance with 35 U.S.C. §101 is a question of fact.[13] The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration.[14] Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant. The issue will then be decided on the totality of evidence.

The well established case law is clearly reflected in the Utility Examination Guidelines ("Utility Guidelines"),[15] which acknowledge that an invention complies with the utility requirement of 35 U.S.C. §101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility." Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic without also identifying the conditions that are to be diagnosed.

In explaining the "substantial utility" standard, M.P.E.P. §2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the

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[10] *Ibid.*

[11] *In re Langer*, 503 F.2d 1380,1391, 183 U.S.P.Q. (BNA) 288, 297 (C.C.P.A. 1974).

[12] *See also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (C.C.P.A. 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (C.C.P.A. 1977).

[13] *Raytheon v. Roper*, 724 F.2d 951, 956, 220 U.S.P.Q. (BNA) 592, 596 (Fed. Cir. 1983) *cert. denied,* 469 US 835 (1984).

[14] *In re Oetiker*, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d (BNA) 1443, 1444 (Fed. Cir. 1992).

[15] 66 Fed. Reg. 1092 (2001).

public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Appellant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial utility.'"[16] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[17] gives the following instruction to patent examiners: "If the Appellant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

ii) The Data and Documentary Evidence Supporting a Patentable Utility

Patentable utility for the PRO274 polypeptides and their antibodies is based upon the gene amplification data for the gene encoding the PRO274 polypeptide of SEQ ID NO: 7. Appellants respectfully submit that the data presented in Example 114 of the specification and the cumulative evidence of record support a "specific, substantial and credible" asserted utility for the presently claimed invention.

Example 114 describes the results obtained using a very well-known and routinely employed polymerase chain reaction (PCR)-based assay, the TaqMan™ PCR assay, also referred to herein as the gene amplification assay. This assay allows one to quantitatively measure the level of gene amplification in a given sample, say, a tumor extract, or a cell line. It was well known in the art at the time the invention was made that gene amplification is an essential mechanism for oncogene activation. Appellants isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9, including primary lung cancers of the type and stage indicated in Table 8 of the specification. The tumor samples were tested in triplicates with Taqman™ primers and with internal controls, beta-actin and GADPH in order to quantitatively compare DNA levels between samples. As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control and also, no-template controls. Gene amplification was monitored using real-time quantitative

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[16] M.P.E.P. §2107.01.

[17] M.P.E.P. §2107 II(B)(1).

TaqMan™ PCR. Table 9 shows the resulting gene amplification data. Further, Example 114 explains that the results of TaqMan™ PCR are reported in ΔCt units, wherein **one unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Appellants respectfully submit that a ΔCt value of at least 1.0, which is a **more than 2-fold increase**, was observed for PRO274 in primary lung tumors LT4, LT16, and LT18. PRO274 showed approximately 1.00-1.61 ΔCt units which corresponds to $2^{1.00}$ -$2^{1.61}$ fold, or 2.0-3.1 fold amplification in three different human primary lung tumors, which is significant and thus the PRO274 gene has utility as a diagnostic marker of lung cancer.

It is also well known that gene amplification occurs in most solid tumors, and generally is associated with poor prognosis.

In support, Appellants have submitted, in their Response filed September 14, 2004, a Declaration by Dr. Audrey Goddard. Appellants particularly draw the Board's attention to page 3 of the Goddard Declaration which clearly states that:

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy. (Emphasis added).

As indicated above, the gene encoding the PRO274 polypeptide shows significantly higher than a two fold amplification in three different lung tumors. In addition, the Goddard Declaration clearly establishes that the TaqMan real-time PCR method described in Example 114 has gained wide recognition for its versatility, sensitivity and accuracy, and is in extensive use for the study of gene amplification. The facts disclosed in the Declaration also confirm that based upon the gene amplification results, one of ordinary skill would find it credible that PRO274 is a diagnostic marker of lung cancer.

Further, as discussed in detail below, Appellants have provided ample evidence in the form of articles from the art, like Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and over a 100

references (see Evidence List items 13-144) and Declarations by experts in the field of oncology and gene expression, i.e.: the Declarations by Dr. Paul Polakis (I and II) and by Dr. Avi Ashkenazi, to show that, in general, if a gene is amplified in cancer, it is "more likely than not" that the encoded protein will also be expressed at an elevated level.

The Examiner has asserted that "the specification provides data showing a very small increase in DNA copy number, approximately 2-fold, in a few tumor samples for PRO274." (Page 4 of the Office Action mailed July 19, 2005). The Examiner further asserts that "it was imperative to find evidence in the relevant scientific literature whether or not a small increase in DNA copy number would be considered by the skilled artisan to be predictive of increased mRNA and polypeptide levels." (Page 4 of the Office Action mailed July 19, 2005).

Appellants respectfully submit that the Examiner seems to be applying a heightened utility standard in this instance, which is legally incorrect. Appellants have shown that the gene encoding PRO274 demonstrated significant amplification, from 2.0-3.1 fold, in three lung tumors. As explained in the Declaration of Dr. Audrey Goddard (submitted with the Response filed September 14, 2004):

> It is further my considered scientific opinion that an at least **2-fold increase** in gene copy number in a tumor tissue sample relative to a normal (*i.e.*, non-tumor) sample **is significant** and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. (Emphasis added).

By referring to the 2.0-fold to 3.1-fold amplification of the PRO274 gene in lung tumors as "very small" the Examiner appears to ignore the teachings within an expert's declaration without any basis, or without presenting any evidence to the contrary. Appellants respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part IIB, 66 Fed. Reg. 1098 (2001)) which state that:

> "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered".

Thus, barring evidence to the contrary, Appellants maintain that the 2.2 to 3.1-fold amplification disclosed for the PRO274 gene is significant and forms the basis for the utility claimed herein.

The Examiner has further asserted that "[g]iven that PRO274 was amplified in only a very small number of tumors of the same type, the data do not support the implicit conclusion of the specification that PRO274 shows a positive correlation with lung cancer, much less that the levels of PRO274 would be diagnostic of such." (Page 6 of the Office Action mailed May 20, 2004).

Appellants emphasize that they have shown significant DNA amplification in three out of the lung tumor samples in Table 9, Example 114 of the instant specification. The fact that not all lung tumors tested positive in this study does not make the gene amplification data less significant. As any skilled artisan in the field of oncology would easily appreciate, not all tumor markers are generally associated with every tumor, or even, with most tumors. For example, the article by Hanna and Mornin (submitted with the Response filed September 14, 2004), discloses that the known breast cancer marker HER-2/neu is "amplified and/or overexpressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinoma" (page 1, col. 1). In fact, some tumor markers are useful for identifying rare malignancies. That is, the association of the tumor marker with a particular type of tumor lesion may be rare, or, the occurrence of that particular kind of tumor lesion itself may be rare. In either event, even these rare tumor markers which do not give a positive hit for most common tumors, have great value in tumor diagnosis, and consequently, in tumor prognosis. The skilled artisan would certainly know that such tumor markers are useful for better classification of tumors. Therefore, whether the PRO274 gene is amplified in three lung tumors or in all lung tumors is not relevant to its identification as a tumor marker, or its patentable utility. Rather, the fact that the amplification data for PRO274 is considered significant is what lends support to its usefulness as a tumor marker.

The Examiner has asserted that "[t]he data presented in the specification were not corrected for aneuploidy" and cites a reference by Sen *et al.* in support of the assertion that "[a] slight amplification of a gene does not necessarily mean overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid." (Page 6 of the Office Action mailed May 20, 2005).

Appellants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Appellants' Response filed September 14, 2004),

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Appellants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

The Examiner has asserted that "[o]ne skilled in the art would do further research to determine whether or not the PRO274 polypeptide levels increased significantly in the tumor samples. The requirement for such further research makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial." (Page 4 of the Office Action mailed July 19, 2005).

As discussed above, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, any reasonable use that an Appellant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a 'substantial' utility."[18] Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement,[19] gives the following instruction to patent examiners: "If the Appellant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

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[18] M.P.E.P. §2107.01.

[19] M.P.E.P. §2107 II(B)(1).

Appellants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO274 is significantly amplified in certain lung tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO274 gene is amplified, the PRO274 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO274 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO274 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed antibodies that bind to the PRO274 polypeptide, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Appellants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO274 polypeptide expression and that the claimed antibodies which bind the PRO274 polypeptide have utility in the diagnosis of cancer.

iii) A *prima facie* case of lack of utility has not been established

Appellants submit that the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Appellant.

The Examiner has asserted that "it does not necessarily follow that an increase in gene copy number results in increased gene expression and increased protein expression, such that antibodies would be useful diagnostically." (Page 7 of the Office Action mailed May 20, 2004). In support of these assertions, the Examiner referred to Pennica *et al.* and contended that "Pennica *et al.* was cited as evidence showing a lack of correlation between gene (DNA) amplification and mRNA levels." (Page 4 of the Office Action mailed July 19, 2005). The

Examiner further referred to Gygi *et al.*, and asserted that "Gygi *et al.* was cited as providing evidence that polypeptide levels cannot be accurately predicted from mRNA levels." (Page 4 of the Office Action mailed July 19, 2005).

As a preliminary matter, Appellants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels, or that protein levels can be "accurately predicted." As discussed above, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Appellants submit that in order to overcome the presumption of truth that an assertion of utility by the Appellant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist**. Appellants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Pennica *et al.*

The Examiner cited the abstract of Pennica *et al.* for its disclosure that "WISP-1 gene amplification and overexpression in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient." From this, the Examiner correctly concluded that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty.

In fact, as noted even in Pennica *et al.*, "[a]n analysis of *WISP*-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*" (Pennica *et al.*, page14722, left column, first full paragraph, emphasis added). Thus the findings of Pennica *et al.* with respect to WISP-1 support Appellants' arguments. In the case of WISP-3, the authors report that there was no change in the DNA copy number, but there was a change in mRNA levels. This apparent lack of correlation between DNA and mRNA

levels is not contrary to Appellants' assertion that a change in DNA copy number generally leads to a change in mRNA level. Appellants are not attempting to predict the DNA copy number based on changes in mRNA level, and Appellants have not asserted that the only means for changing the level of mRNA is to change the DNA copy number. Therefore a change in mRNA without a change in DNA copy number is not contrary to Appellants' assertions.

The fact that the single WISP-2 gene did not show the expected correlation of gene amplification with the level of mRNA/protein expression does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the WISP-2 gene is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, as was demonstrated for WISP-1.

Accordingly, Appellants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Gygi *et al.*

The Examiner further cited the Gygi *et al.* reference to establish that "the protein levels cannot be accurately predicted from the level of the corresponding mRNA transcript." The Examiner adds that "Gygi *et al.* ... studied over 150 proteins... and found no strong correlation between proteins and transcript levels." (Page 7 of the Office Action mailed May 20, 2004).

Appellants respectfully traverse and point out that, on the contrary, Gygi *et al.* never indicate that the correlation between mRNA and protein levels does not exist. Gygi *et al.* only state that the correlation may not be sufficient in **accurately** predicting protein level from the level of the corresponding mRNA transcript (Emphasis added) (see page 1270, Abstract). This result is expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, Gygi *et al.* concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA

transcript in a single cellular stage or type when looking at the level of transcripts across different genes.

Importantly, Gygi *et al.* did not say that for a single gene, a change in the level of mRNA transcript is not positively correlated with a change in the level of protein expression. Appellants have asserted that increasing the level of mRNA for a particular gene leads to a corresponding increase for the encoded protein. Gygi *et al.* did not study this issue and says absolutely nothing about it. One cannot look at the level of mRNA across several different genes to investigate whether a change in the level of mRNA for a particular gene leads to a change in the level of protein for that gene. Therefore, Gygi *et al.* is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the PTO's rejection of Appellants' asserted utility.

Furthermore, Appellants note that contrary to the Examiner's statement, the Gygi data indicate **a general trend** of correlation between protein [expression] and transcript levels (Emphasis added). For example, as shown in Figure 5, an mRNA abundance of **250-300** copies /cell correlates with a protein abundance of **500-1000** x 10^3 copies/cell. An mRNA abundance of **100-200** copies/cell correlates with a protein abundance of **250-500** x 10^3 copies/cell (emphasis added). Therefore, high levels of mRNA **generally** correlate with high levels of proteins. In fact, most data points in Figure 5 did not deviate or scatter away from the general trend of correlation. Thus, the Gygi data meets the "more likely than not standard" and shows that a positive correlation exists between mRNA and protein. Therefore, Appellants submit that the Examiner's rejection is based on a misrepresentation of the scientific data presented in Gygi *et al.*

Gygi *et al.* may teach that protein levels cannot be "accurately predicted" from mRNA levels in the sense that the exact numerical amounts of protein present in a tissue cannot be determined based upon mRNA levels. Appellants respectfully submit that the Office Action's emphasis on the need to "accurately predict" protein levels based on mRNA levels misses the point. The asserted utility for the claimed polypeptides is in the diagnosis of cancer. What is relevant to use as a cancer diagnostic is relative levels of gene or protein expression, not absolute values, that is, that the gene or protein is differentially expressed in tumors as compared to normal tissues. Appellants need only show that there is a correlation between DNA, mRNA, and protein levels, such that gene amplification and mRNA overexpression generally predict protein overexpression. A showing that mRNA levels can be used to "accurately predict" the precise levels of protein expression is not required.

In conclusion, the Examiner has not shown that a lack of correlation between gene amplification: polypeptide over-expression, as observed for the *WISP-2* gene, is typical. In fact, contrary to what the Examiner contends, the art indicates that, if a gene is amplified in cancer, it is **more likely than not** that the encoded protein will be expressed at an elevated level. As noted even in Pennica *et al.*, a correlation between DNA amplification: polypeptide over-expression was observed in the case of *WISP-1* and similarly, in Gygi *et al.*, **most genes** showed a correlation between mRNA levels and protein levels. Since the standard is not absolute certainty, a *prima facie* showing of lack of utility has not been made in this instance.

Hu *et al.*

The Examiner further cited Hu *et al.* to the effect that genes displaying a 5-fold change or less in mRNA expression in tumors compared to normal showed no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease. (Page7 of the Office Action mailed July 19, 2005).

Appellants first note that the title of Hu *et al.* is "Analysis of Genomic and Proteomic Data Using Advanced Literature Mining." As the title clearly suggests, the conclusion suggested by Hu *et al.* is merely based on a statistical analysis of the information disclosed in the published literature. As Hu *et al.* states, "We have utilized a computational approach to literature mining to produce a comprehensive set of gene-disease relationships." In particular, Hu *et al.* relied on the MedGene Database and the Medical Subject Heading (MeSH) files to analyze the gene-disease relationship. More specifically, Hu *et al.* "compared the MedGene breast cancer gene list to a gene expression data set generated from a micro-array analysis comparing breast cancer and normal breast tissue samples." (See page 408, right column). Therefore, Appellants first submit that the reference by Hu *et al.* only studies the statistical analysis of micro-array data and not gene amplification data. Thus their findings would not be directly applicable to gene amplification data.

According to Hu *et al.*, "*different* statistical methods" were applied to "*estimate* the strength of gene-disease relationships and evaluated the results." (See page 406, left column, emphasis added). Using these different statistical methods, Hu *et al.* "[a]ssessed the relative

strengths of gene-disease relationships based on the frequency of both co-citation and single citation." (See page 411, left column). It is well known in the art that various statistical methods allow different variables to be manipulated to affect the outcome. For example, the authors admit, "Initial attempts to search the literature using" the list of genes, gene names, gene symbols, and frequently used synonyms, generated by the authors "revealed several sources of false positives and false negatives." (See page 406, right column). The authors further admit that the false positives caused by "duplicative and unrelated meanings for the term" were "difficult to manage." Therefore, in order to minimize such false positives, Hu *et al.* disclose that these terms "had to be eliminated entirely, thereby reducing the false positive rate but unavoidably under-representing some genes." *Id.* Hence, Appellants respectfully submit that in order to minimize the false positives and negatives in their analysis, Hu *et al.* manipulated various aspects of the input data.

Appellants further submit that the statistical analysis by Hu *et al.* is not a reliable standard because the frequency of citation reflects only the current research interest of a molecule rather than the true biological function of the molecule. Indeed, the authors acknowledge that "[r]elationship established by frequency of co-citation do not necessarily represent a true biological link." (See page 411, right column). One would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a published or known role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and say nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Even assuming that Hu *et al.* provide evidence to support a true relationship, the conclusion in Hu *et al.* only applies to a specific type of breast tumor (estrogen receptor (ER)-positive breast tumor) and can not be generalized as a principle governing microarray study of breast cancer in general, let alone the various other types of cancer genes in general. In fact, even Hu *et al* admit that., "[i]t is likely that this threshold will change depending on the disease as well as the experiment. Interestingly, the observed correlation was only found among ER-

positive (breast) tumors not ER-negative tumors." (See page 412, left column). Therefore, based on these findings, the authors add, "This may reflect a bias in the literature to study the more prevalent type of tumor in the population. Furthermore, this emphasizes that caution must be taken when interpreting experiments that may contain subpopulations that behave very differently." *Id.* (Emphasis added).

More importantly, Hu *et al.* did not look for a correlation between changes in mRNA and changes in protein levels, and therefore their results are not contrary to Appellants' assertion that there is a correlation between the two. Appellants are not relying on any "biological role" that the PRO274 polypeptide has in cancer for its asserted utility. Instead, Appellants are relying on the amplification of the gene encoding PRO274 in certain tumors compared to their normal tissue counterparts. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as a diagnostic marker of cancer.

Li *et al.*

The Examiner also cites Li *et al.* as teaching that "68.8% of the genes showing over-representation in the genome did not show elevated transcript levels." (Page 13 of the Office Action mailed November 1, 2006). Appellants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that "[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma" (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Appellants' previous responses, and in the Goddard Declaration of record, an appropriate threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above the PRO274 gene showed 2.0 fold to 3.05-fold amplification in three different lung tumors, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not

disprove that a gene with a substantially higher level of gene amplification, such as PRO274, would be expected to show a corresponding increase in transcript expression. Appellants point out that the Examiner has found these arguments persuasive as noted in the Advisory Action mailed March 1, 2007.

Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.*

In further support of the assertion that "*changes* in mRNA expression frequently do not result in *changes* in protein expression" (page 16 of the Office Action mailed November 1, 2006; emphasis in original), the Examiner cites three additional references, by Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.*

The Examiner cites Nagaraja *et al.* as allegedly teaching that in comparisons of expression profiles for normal breast compared to breast cancer, "the proteomic profiles indicated altered abundance of fewer proteins as compared to transcript profiles." (Page 15 of the Office Action mailed November 1, 2006).

Appellants respectfully submit that the fact that many more transcripts than proteins were found to be differentially expressed does not mean that most mRNA changes did not result in correlating protein changes, but merely reflects the fact that expression levels were only measured at all for many fewer proteins than transcripts. In particular, the total number of proteins whose expression levels could be visualized on silver-stained gels was only about 300 (page 2332, col. 1), as compared to the approximately 14,500 genes on the microarray chips for which mRNA levels were measured (page 2336, col. 1). Since the expression levels of so many fewer proteins than transcripts were measured, it is hardly surprising that a smaller absolute number of proteins than mRNAs were found to be overexpressed, because the protein products of most of the overexpressed mRNAs would not have been among the small number of proteins identified on the gels.

The Examiner next cites Waghray *et al.*, to the effect that "for most of the proteins identified, there was no appreciable concordant change at the RNA level." (Page 15 of the Office Action mailed November 1, 2006).

Appellants emphasize that Appellants are asserting that a measurable change in mRNA level generally leads to a corresponding change in the level of protein expression, not that changes in protein level can be used to predict changes in mRNA level. Waghray *et al.* did not

take genes which showed significant mRNA changes and check the corresponding protein levels. Instead, the authors looked at a small and unrepresentative number of proteins, and checked the corresponding mRNA levels. Waghray *et al.* acknowledge that only "[a] relatively small set of genes could be analyzed at the protein level, largely due to the limited sensitivity of 2-D PAGE" (page 1337, col. 1). In particular, while the authors examined the expression levels of16,570 genes (page 1329, col. 2), they were able to measure the expression levels of only 1031 proteins (page 1333, col. 2). Waghray *et al.* does not teach that changes in mRNA expression were not correlated with changes in expression of the corresponding protein. All Waghray *et al.* state is that "for most of the proteins identified, there was no appreciable concordant change at the mRNA level" (page 1337, col. 2). This statement is not relevant to Appellants' assertion of utility, since Appellants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. Waghray *et al.* do not contradict Appellants' assertion that changes in mRNA expression, in general, correspond to changes in expression of the corresponding protein. Of note, the Examiner has withdrawn the rejection based on Waghray et al. in the Advisory Action of March 1, 2007.

Lastly, the Examiner cites Sagynaliev *et al.*, as allegedly teaching that "it is also difficult to reproduce transcriptomics results with proteomics tools." In particular, the Examiner notes that according to Sagynaliev *et al.*, of 982 genes found to be differentially expressed in *Hu*man CRC, only 177 (18%) have been confirmed using proteomics technologies. (Page 16 of the Office Action mailed November 1, 2006).

The Sagynaliev *et al.* reference, titled "Web-based data warehouse on gene expression in *Hu*man colorectal cancer" (emphasis added), drew conclusions based upon a literature survey of gene expression data published in *Hu*man CRC, and not from experimental data. While a literature survey can be a useful tool to assist researchers, the results may greatly over-represent or under-represent certain genes, and thus the conclusions may not be generally applicable. In particular, Appellants note that, as evidenced by Nagaraja *et al.* and Waghray *et al.*, discussed above, the number of mRNAs examined in transcriptomics studies is typically much larger than the number of proteins examined in corresponding proteomics studies, due to the difficulties in detecting and resolving more than a small minority of all expressed proteins on 2D gels. Thus, the fact that only 18% of all genes found to be differentially expressed in *Hu*man CRC have been confirmed using proteomics technologies does not mean that the corresponding proteins are not also differentially

expressed, but is most likely due to the fact that the corresponding proteins were not identified on 2D gels, and thus their expression levels remain unknown.

The authors of Sagynaliev *et al.* acknowledge the many technical problems in finding proteomic data for CRC that can be matched to transcriptomic data to see if the two correlate. The authors state that "results have been obtained using heterogeneous samples in particular cell lines, whole tissue biopsies, and epithelial cells purified from surgical specimens." However, "Results obtained in cell lines do not allow accurate comparison between normal and cancer cells, and the presence/absence of proteins of interest has to be confirmed in biopsies." (Page 3072, left column.) In particular, the authors specifically note that "only a single study [1] provided differential display protein expression data obtained in the *Hu*man patient, using whole tissue biopsy." (Page 3068, left column, second paragraph; *see also*, Table 2.) The examiner also notes and the authors state, "For CRC, there is no publication comparing mRNA and protein expression for a cohort of genes." (Page 3077, left column, last paragraph, emphasis added.)

Appellants further note that Table 2 shows that 6 out of 8 published proteomics studies were done using 2-D PAGE. However, the authors state that "2-D PAGE or 2-D DIGE have well-known technological limitations ... even under well-defined experimental conditions, 2-D PAGE parallel analysis of paired CRC samples is hampered by a significant variability." (Page 3077, left column, third paragraph.) Therefore, Appellants respectfully submit that it is well known in the art that there are problems associated with selecting only those proteins detectable by 2D gels.

The Examiner further asserts that "the specification of the instant application does not teach a change in mRNA level of PRO274" because "[t]here are no teachings in the specification as to the differential expression of PRO274 mRNA in the progression of lung cancer or in response to different treatments of hormones (for example)." (Page 16 of the Office Action mailed November 1, 2006). Appellants respectfully note that the instant specification measured gene amplification, not mRNA expression. Appellants further submit that it is well known that cancers arise from the transformation of normal tissue cells to cancerous cells, *thus* the observed differences in gene amplification between normal and cancerous tissues are in fact the result of previously occurring changes.

Finally, in the Advisory Action of March 1, 2007, the Examiner notes that Sagynaliev points out that many genes found to be differentially regulated do not play a causal role in CRC carcinogenesis.

The Examiner appears to be concerned with the underlying mechanism resulting in the positive gene amplification results, and not with those results themselves. However, the Examiner's concerns regarding the causal role of PRO274 associated with any type of cancer versus normal tissue, in no way negate the utility of the claimed invention. Appellants are relying on diagnostic utility and not therapeutic utility. The fact remains that the gene amplification results demonstrate overexpression of PRO274 in the named tumor. One of ordinary skilled in the art does not need to know the underlying mechanism of the overexpression of PRO274, or the downstream effects of that overexpression, to practice the diagnostic utility. One of ordinary skill in the art, in possession of these results, would have believed it more likely than not that the PRO274 polypeptide and the antibodies that binds it were useful for their asserted utility.

In summary, Appellants respectfully submit that the Examiner has not shown that a change in gene expression level in tumor as compared to normal tissue is not correlated with a change in protein expression. The Patent Office has failed to meet its initial burden of proof that Appellants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the Pennica *et al.*, Gygi *et al.* and Hu *et al.* articles, as well as those by Li *et al.*, Nagaraja *et al.*, Waghray *et al.*, and Sagynaliev *et al.*, do not provide sufficient reasons to doubt the statements by Appellants that PRO274 has utility. As discussed above, the law does not require that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels. Therefore, Appellants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited references and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

iv) It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Appellants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Appellants' Response filed September 14, 2004) collectively teach that in general, gene amplification increases mRNA expression.

Second, Appellants have submitted over a *Hu*ndred references, along with Declarations of Dr. Paul Polakis with their Preliminary Amendment filed on August 3, 2006, which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Third, Appellants would like to bring to the Examiner's attention a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469). In its decision, the Board reversed the utility rejection, acknowledging that "there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that." (Page 9 of the Decision). Appellants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO274 polypeptide to refute Appellants' assertion of a correlation between mRNA levels and protein expression.

Thus, taken together, all of the submitted evidence supports Appellants' position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

Appellants submit that there are numerous articles which show that generally, if a gene is amplified in cancer, it is more likely than not that the mRNA transcript will be expressed at an elevated level. For example, Orntoft *et al.* (*Mol. and Cell. Proteomics*, 2002, vol. 1, pages 37-45 - made of record in Appellants' Response filed September 14, 2004) studied transcript levels of 5600 genes in malignant bladder cancers, many of which were linked to the gain or loss of chromosomal material using an array-based method. Orntoft *et al.* showed that there was a gene dosage effect and taught that "in general (18 of 23 cases) chromosomal areas with more than 2-fold gain of DNA showed a corresponding increase in mRNA transcripts" (see column 1, abstract). In addition, Hyman *et al.* (*Cancer Res.*, 2002, vol. 62, pages 6240-45 - made of record in Appellants' Response filed September 14, 2004) showed, using CGH analysis and cDNA microarrays which compared DNA copy numbers and mRNA expression of over 12,000 genes in breast cancer tumors and cell lines, that there was "evidence of a prominent global influence of copy number changes on gene expression levels." (See page 6244, column 1, last paragraph). Additional supportive teachings were also provided by Pollack *et al.*, (*PNAS*, 2002, vol. 99, pages 12963-12968 - made of record in Appellants' Response filed September 14, 2004) who studied a series of primary *Hu*man breast tumors and showed that "...62% of highly amplified genes show moderately or highly elevated expression, and DNA copy number influences gene

expression across a wide range of DNA copy number alterations (deletion, low-, mid- and high-level amplification), and that on average, a 2-fold change in DNA copy number is associated with a corresponding 1.5-fold change in mRNA levels." Thus, these articles collectively teach that in general, gene amplification increases mRNA expression.

Upon consideration of Appellants arguments made in the response of February 1, 2007. the Examiner states in the Advisory Action mailed March 1, 2007 that the articles by Ornitoft *et al.*, Hyman *et al.*, and Pollack *et al.* "are convincing that gene amplification generally results in increased transcription."

In addition, in their Responses filed September 14, 2004 and August 3, 2006, Appellants submitted two Declaration by Dr. Polakis, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general. As Dr. Polakis explains, the primary focus of the microarray project was to identify tumor cell markers useful as targets for both the diagnosis and treatment of cancer in *Hu*mans. The Declaration by Dr. Paul Polakis (Polakis I - made of record in Appellants' Response filed September 14, 2004) explains that in the course of Dr. Polakis' research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in *Hu*man tumor cells at significantly higher levels than in corresponding normal *Hu*man cells. Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels. The second Declaration by Dr. Polakis (Polakis II- - made of record in Appellants' Response filed August 3, 2006) presented evidentiary data in Exhibit B. Exhibit B of the Declaration identified 28 gene transcripts out of 31 gene transcripts (*i.e.*, greater than 90%) that showed good correlation between tumor mRNA and tumor protein levels. As Dr. Polakis' Declaration (Polakis II) says "[a]s such, in the cases where we have been able to quantitatively measure both (i) mRNA and (ii) protein levels in both (i) tumor tissue and (ii) normal tissue, we have observed that in the vast majority of cases, there is a very strong correlation between increases in mRNA expression and increases in the level of protein encoded by that mRNA." Accordingly, Dr. Polakis has provided the facts to enable the Examiner to draw independent conclusions regarding protein data. Appellants further emphasize that the opinions expressed in the Polakis Declaration, including in the above quoted statement, are all based on factual findings. For instance, antibodies binding to about 30 of these tumor antigens were prepared and

mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when *Hu*man tumor cells are compared with their corresponding normal cells. Therefore, Dr. Polakis' research, which is referenced in his Declaration, shows that, in general, there is a correlation between increased mRNA and polypeptide levels. Hence, one of skill in the art would reasonably expect that, based on the gene amplification data of the PRO274 gene, the PRO274 polypeptide is concomitantly overexpressed in lung tumors studied as well. Based on these experimental data and his vast scientific experience of more than 20 years, Dr. Polakis states that, for *Hu*man genes, increased mRNA levels typically correlate with an increase in abundance of the encoded protein. He further confirms that "it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein."

Appellants further note that the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (i.e., that it is more likely than not informative of the protein level).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.,* Hyman *et al.,* Pollack *et al.,* and the Polakis Declaration, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Thus, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed. Accordingly, Appellants submit that the PRO274 polypeptides and antibodies have utility in the diagnosis of cancer and based on such a utility, one of skill in the art would know exactly how to use the claimed antibodies for diagnosis of cancer.

With respect to the correlation between mRNA expression and protein levels, the Examiner asserts that the Polakis Declaration (Polakis I) is insufficient to overcome the rejection of claims 58-62 since it is limited to a discussion of data regarding the correlation of mRNA

levels and polypeptide levels and not gene amplification levels. The Examiner asserts that the Declaration does not provide data such that the Examiner can independently draw conclusions. (Page 7 of the Office Action mailed July 19, 2005).

Appellants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* articles. Appellants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when Human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew.[20] "After evidence or argument is submitted by the Appellant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument"[21] Furthermore, the Federal Court of Appeals held in *In re Alton*, "[W]e are aware of no reason why opinion evidence relating to a fact issue should not be considered by an examiner."[22] Appellants also respectfully draw the Examiner's attention to the Utility Examination Guidelines[23] which

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[20] *In re Rinehart,* 531 F.2d 1084, 189 U.S.P.Q. 143 (C.C.P.A. 1976); *In re Piasecki,* 745 F.2d. 1015, 226 U.S.P.Q. 881 (Fed. Cir. 1985).

[21] *In re Alton,* 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996)(quoting *In re Oetiker,* 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992)).

[22] *Id.* at 1583.

[23] Part IIB, 66 Fed. Reg. 1098 (2001).

state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." The statement in question from an expert in the field (the Polakis Declaration) states that "it is my considered scientific opinion that for Human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." Therefore, barring evidence to the contrary regarding the above statement in the Polakis Declaration, this rejection is improper under both the case law and the Utility guidelines.

The Examiner asserts that the second Polakis Declaration (Polakis II) is insufficient to overcome the utility rejection because PRO274 does not appear in the table (Exhibit B), and allegedly it is not clear whether PRO274 shares the same characteristics as those tumor antigens tested. (Page 5 of the Office Action mailed November 1, 2006).

Appellants respectfully submit that, as discussed in their previous Responses and Appeal Brief, the standard for utility is more likely than not. Dr. Polakis' Declarations provide evidence, in the form of statements by an expert in the art, that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell." The PRO274 gene was found to be amplified in lung tumors. As discussed above and in Appellants' previous Responses, one of ordinary skill in the art would therefore expect the PRO274 mRNA to be overexpressed in the same *Hu*man lung tumor samples. Accordingly, one of ordinary skill in the art would understand that the PRO274 polypeptide would be expected (more likely than not) to be overexpressed in *Hu*man lung tumor samples relative to their normal *Hu*man tissue counterparts, as are the majority of other molecules tested.

The Examiner further states that "levels of mRNA and protein in tumor tissue were compared to corresponding normal tissue, but the amplification levels of genomic DNA from example 114 were compared to normal *Hu*man blood, not corresponding normal tissue." (Page 5 of the Office Action mailed November 1, 2006). Appellants respectfully note that the Polakis Declaration describes the results of microarray experimentation, while Example 114 of the specification discloses gene amplification data. T*Hu*s the Examiner's attempt to contrast the methodology of the two types of experiments is misplaced.

The Examiner appears to require Appellants to provide every single experimental detail involved in the testing of the mRNA/protein correlation according to the Polakis Declaration. Such a requirement is unreasonable because neither the law nor the Utility Guidelines requires Appellants to do so.

The Examiner further notes (at page 6 of the Office Action mailed November 1, 2006) that Dr. Polakis is employed by the assignee. Appellants respectfully submit that note the sworn Declaration of Dr. Polakis is sufficient to support Appellants' position a general mRNA/protein correlation, even if Dr. Polakis is an employee of the assignee.

Based on the above arguments, Appellants have clearly demonstrated a credible, specific and substantial asserted utility for the PRO274 polypeptide and the claimed antibodies that bind them, for example, as diagnostic markers for lung tumors. Further, based on this utility and the disclosure in the specification, one skilled in the art at the time the application was filed would know how to use the claimed antibodies.

With respect to the over one *Hu*ndred additional references supporting a correlation between mRNA and protein overexpression cited in Appellants' Preliminary Amendment filed August 3, 2006, the Examiner asserts that "[w]ith the exception of Futcher *et al.*, all of Appellant's newly cited references are directed to the analysis of single genes, or a small group of genes, and therefore do not demonstrate trends found across proteins in general." (Page 8 of the Office Action mailed November 1, 2006).

Appellants note that the submitted references, which represent experiments conducted by a large number of different research groups, demonstrate a trend of correlation found across proteins in general, and that this trend is confirmed by an overwhelming number of experiments by different researchers, using diverse experimental designs, testing various types of tissues, under numerous biological conditions. Although only a single gene or a small group of genes was tested by each individual study group, the cumulative evidence generated by over one *Hu*ndred study groups certainly establishes that it is well-accepted in the art that a general mRNA/protein correlation exists.

In response to the submitted textbook excerpts by Alberts and Lewin (submitted in the IDS filed on August 3, 2006 in Exhibit 1), the Examiner acknowledges that the teachings of Alberts and Lewin support that the initiation of transcription is the most common point for a cell to regulate gene expression. The Examiner asserts, however, that the initiation of transcription

"is not the only means of regulating gene expression" according to the teaching of Alberts. (Page 7 of the Office Action mailed November 1, 2006).

Appellants respectfully submit that the utility standard is not **absolute certainty**. Rather, to overcome the presumption of truth that an assertion of utility by an Appellant enjoys, the PTO must establish that it is **more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, Appellants **do not need** to establish that transcription initiation is **the only means** of regulating gene expression in order to meet the utility standard. Instead, as long as it is the most common point of regulation, as admitted by the Examiner, it would be more likely than not that a change in the transcription level of a gene gives rise to a change in translation level of a gene. Appellants note that both Alberts and Lewin make clear that it is far more likely than not that protein levels for any given gene are regulated at the transcriptional level. Alberts, for example, states that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Cell 4th at 379 (emphasis added). In a similar vein, Lewin states that "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added). Thus, the utility standard is met.

With respect to Appellants' arguments regarding Meric *et al.* (submitted in the IDS filed on August 3, 2006 in Exhibit 1), the Examiner asserts that Meric teaches that "gene expression is quite complicated, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." (Page 8 of the instant Office Action).

Appellants respectfully submit that Meric simply summarizes the translational regulation of cancer cells. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth. Meric further discusses how alterations in translation control occur in cancer. For example, variant mRNA sequences can alter the translational efficiency of individual mRNA molecules. (see Abstract). Meric further teaches that the changes in translational efficiency of a mRNA transcript depend on the mutation of a specific mRNA sequence. (Page 973, column 2 to page 974, column 1). Meric never suggests that the translation of a cancer gene is suppressed in cancer in general, and that therefore, increased mRNA levels will not, in general, yield increased

protein levels. To the contrary, Meric teaches that the translation efficiency of a number of cancer genes is enhanced in cancer cells compared to their normal counterparts. For instance, in patients with multiple myeloma, a C-T mutation in the c-myc IRES was identified and found to cause an enhanced initiation of translation (page 974, column 1). Therefore the level of proteins encoded by these genes increases in cancer cells at an even higher magnitude than the corresponding mRNA level. T*Hus* Meric clearly supports Appellants' assertions that it is more likely than not that, in general, changes in mRNA levels are correlated with changes in protein levels.

The Examiner further alleges that Meric teaches "translational efficiency of a number of cancer genes is enhanced in cancer cells compare to its normal counterpart due to mutation" and from this asserts that "the specification does not teach that PRO274 mRNA in cancer cells have a mutation that would lead to increased translation." (Advisory Action mailed March 1, 2007).

Appellants respectfully point out that Meric simply summarizes translational regulatory mechanisms in cancer cells and discusses how alterations in different aspects of translation control occur in cancer. Meric indicates that translation initiation is regulated in response to nutrient availability and mitogenic stimulation and is coupled to cell cycle progression and cell growth. Meric does not teach that mutation of a gene is required for its increased translation in cancer. Appellants do not need to establish the mechanism of regulating PRO274 gene expression in order to meet the utility standard.

The Examiner asserts that "the majority of the newly cited references by Appellants are drawn to genes known or suspected to be over expressed or under expressed in cancers, and that are involved with cell proliferation, differentiation and/or cell adhesion/migration, in which expression of the protein is important in the development and progression of the cancer." (Pages 8-9 of the Office Action mailed November 1, 2006).

Appellants respectfully submit that, in fact, a number of the references submitted with Appellants' IDS filed August 3, 2006, are drawn to proteins that are <u>not</u> members of the above protein categories and have no obvious association with cancer. To list just a few examples, Rudlowski *et al.* examined the expression of glucose transporters 1-4; Papotti *et al.* studied three somatostatin receptors; Van der Wilt *et al.* studied deoxycytidine kinase; and Grenback *et al.* studied galanin.

Appellants further respectfully submit that, as discussed in their previous Responses and

Appeal Brief, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Appellants' Response filed September 14, 2004), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being oncogenes or as having any known functions in the development and progression of cancer. Thus the art of record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis Declarations, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed. Thus, Appellants submit that the PRO274 polypeptide and the claimed antibodies that bind it have utility in the diagnosis of cancer.

v) Even if a *prima facie* case of lack of utility has been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes *arguendo* that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, which Appellants submit is **not** true, a polypeptide encoded by a gene that is amplified in cancer would **still** have a specific, substantial, and credible utility. In support, Appellants respectfully draw the Board's attention to page 2 of the Declaration of Dr. Avi Ashkenazi (submitted with the Response filed September 14, 2004) which explains that,

> even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate

> tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product.

Appellants thus submit that simultaneous testing of gene amplification and gene product over-expression enables more accurate tumor classification, even if the gene-product, the protein, is not over-expressed. This leads to better determination of a suitable therapy. Further, as explained in Dr. Ashkenazi's Declaration, absence of over-expression of the protein itself is crucial information for the practicing clinician. If a gene is amplified in a tumor, but the corresponding gene product is not over-expressed, the clinician will decide not to treat a patient with agents that target that gene product. This not only saves money, but also has the benefit that the patient can avoid exposure to the side effects associated with such agents.

This utility is further supported by the teachings of the article by Hanna and Mornin. (Pathology Associates Medical Laboratories, August (1999); submitted with the Response filed September 14, 2004). The article teaches that the HER-2/neu gene has been shown to be amplified and/or over-expressed in 10%-30% of invasive breast cancers and in 40%-60% of intraductal breast carcinomas. Further, the article teaches that diagnosis of breast cancer includes testing both the amplification of the HER-2/neu gene (by FISH) as well as the over-expression of the HER-2/neu gene product (by IHC). Even when the protein is not over-expressed, the assay relying on both tests leads to a more accurate classification of the cancer and a more effective treatment of it.

The Examiner asserts that "[t]he Hanna reference is not applicable to the instant fact situation, as it deals with a known tumor associated gene, and not with a prospective analysis of the type found in this specification." (Page 9 of the Office Action mailed July 19, 2005). To the contrary, Appellants have clearly shown that the gene encoding the PRO274 polypeptide is amplified in at least three primary lung tumors. Therefore, the PRO274 gene, similar to the HER-2/neu gene disclosed in Hanna *et al.*, is a tumor associated gene. Furthermore, as discussed above, in the majority of amplified genes, the teachings in the art overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO274 gene, that the PRO274 polypeptide is concomitantly overexpressed.

However, even if gene amplification does not result in overexpression of the gene product (*i.e.*, the protein) an analysis of the expression of the protein is useful in determining the course of treatment, as supported by the Ashkenazi Declaration. The Examiner has asserted that "the gene product of the instant invention has not been demonstrated to be involved in cancer. Over-expression of a gene product in a cancer cell does not necessarily mean that the gene product is involved in the cancer and that targeting the gene product would be therapeutic." (Page 9 of the Office Action mailed July 19, 2005). The Examiner appears to view the testing described in the Ashkenazi Declaration and the Hanna paper as experiments involving further characterization of the PRO274 polypeptide itself. In fact, such testing is for the purpose of characterizing not the PRO274 polypeptide, but the tumors in which the gene encoding PRO274 is amplified. Testing of tumor markers such as PRO274 is useful for tumor categorization even if the tested marker is not itself the intended therapeutic target. The PRO274 polypeptide is therefore useful in tumor categorization, the results of which become an important tool in the hands of a physician enabling the selection of a treatment modality that holds the most promise for the successful treatment of a patient.

For the reasons given above, Appellants respectfully submit that the present specification clearly describes, details and provides a patentable utility for the claimed invention. Accordingly, Appellants respectfully request reconsideration and reversal of the rejections of Claims 58-62 under 35 U.S.C. §101.

Issue II: Claims 58-62 satisfy the enablement requirement of 35 U.S.C. §112, first paragraph.

Claims 58-62 stand rejected under 35 U.S.C. §112, first paragraph, allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention." (Page 9 of the Office Action mailed July 19, 2005).

In this regard, Appellants refer to the arguments and information presented above in response to the outstanding rejection under 35 U.S.C. § 101, wherein those arguments are incorporated by reference herein. Appellants respectfully submit that as described above, the PRO274 polypeptide has utility in the diagnosis of cancer and based on such a utility, one of skill

in the art would know exactly how to use the claimed antibodies that bind the PRO274 polypeptide for diagnosis of cancer, without undue experimentation.

Accordingly, Appellants respectfully request reconsideration and reversal of the enablement rejection of Claims 58-62 under 35 U.S.C. §112, first paragraph.

Issue III: Claims 58-62 are patentable under 35 U.S.C. §102(b) over Ho *et al.*

Claims 58-62 stand rejected under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*, Science, Vol. 289, pp 265-270, published July 14, 2000.

Appellants submit that, as discussed above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement Appellants rely on the gene amplification results (Example 114) to establish a credible, substantial and specific asserted utility for the PRO274 polypeptide and the claimed antibodies that bind it. These results were first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000. As discussed above, the disclosure of the instant application, which is similar to that of the earlier-filed application (PCT/US00/03565), provides the support required under 35 U.S.C. §112 for the subject matter of the instant claims. Accordingly, Appellants submit that the subject matter of the instant claims is disclosed in the manner provided by 35 U.S.C. §112 in PCT/US00/03565. Therefore, the effective filing date of this application is February 11, 2000, the filing date of PCT/US00/03565.

The scientific journal article by Ho *et al.* was published on July 14, 2000, which is over five months after the effective filing date of the instant application; hence Ho *et al.* is not prior art.

The Examiner has asserted that the present claims are not entitled to the February 11, 2000, filing date of PCT/US00/03565 because "the gene amplification assay fails to disclose a patentable utility for the antibodies to the protein." (Page 10 of the Office Action mailed July 19, 2005).

In this regard, Appellants refer to the arguments and information presented above in response to the outstanding rejections under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph, for alleged lack of utility and enablement. These arguments are incorporated by reference herein. Appellants respectfully submit that as described above under Issue I, the presently claimed invention is supported by a specific, substantial and credible utility and, therefore, the

present specification teaches one of ordinary skill in the art "how to use" the claimed invention without undue experimentation, as described above.

Accordingly, Appellants respectfully request reconsideration and reversal of the rejection of Claims 58-62 under 35 U.S.C. §102(b) as being anticipated by Ho *et al.*

Issue IV: Claims 59-62 are patentable under 35 U.S.C. §103(a) over Ho *et al.* in view of Janeway *et al.*

Claims 59-62 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Ho *et al.* in view of Immunology, The Immune System in Health and Disease, Third Edition, Janeway and Travers, Ed., 1997.

As discussed above, the effective filing date of this application is February 11, 2000, the filing date of PCT/US00/03565. The scientific journal article by Ho *et al.* was published on July 14, 2000, which is over five months after the effective filing date of the instant application; hence Ho *et al.* is not prior art, and is not available as a reference under 35 U.S.C. §103.

Accordingly, Appellants respectfully request reconsideration and reversal of the rejection of Claims 59-62 under 35 U.S.C. §103(a).

CONCLUSION

For the reasons given above, Appellants submit that the specification discloses at least one patentable utility for the antibodies of Claims 58-62, and that one of ordinary skill in the art would understand how to used the claimed antibodies, for example in the diagnosis of lung tumors. Therefore, Claims 58-62 meet the requirements of 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

Further, this patentable utility for the claimed antibodies was first disclosed in International Application No. PCT/US00/03565, filed February 11, 2000, priority to which is claimed in the instant application. Accordingly, the instant application has an effective priority date of February 11, 2000, and therefore Ho *et al.*, Science, Vol. 289, pp 265-270, published on July 14, 2000, is not prior art and does not anticipate the claims under 35 U.S.C. §102(b) or render the claims obvious under 35 U.S.C. §103(a) in view of Janeway *et al.*

Accordingly, reversal of all the rejections of Claims 58-62 is respectfully requested.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **07-1700** (referencing Attorney's Docket No. **GNE-2630 P1C9**).

Respectfully submitted,

Date: April 11, 2008

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8. CLAIMS APPENDIX A

Claims on Appeal

58. An isolated antibody that specifically binds to the polypeptide of SEQ ID NO:7.

59. The antibody of Claim 58 which is a monoclonal antibody.

60. The antibody of Claim 58 which is a humanized antibody.

61. The antibody of Claim 58 which is an antibody fragment.

62. The antibody of Claim 58 which is labeled.

9. EVIDENCE APPENDIX

1. Declaration of Audrey Goddard, Ph.D. under 35 C.F.R. §1.132, with attached Exhibits A-G:

    A. Curriculum Vitae of Audrey D. Goddard, Ph.D.
    B. Higuchi, R. *et al.*, "Simultaneous amplification and detection of specific DNA sequences," *Biotechnology* 10:413-417 (1992).
    C. Livak, K.J., *et al.*, "Oligonucleotides with fluorescent dyes at opposite ends provide a quenched probe system useful for detecting PCR product and nucleic acid hybridization," *PCR Methods Appl.* 4:357-362 (1995).
    D. Heid, C.A. *et al.*, "Real time quantitative PCR," *Genome Res.* 6:986-994 (1996).
    E. Pennica, D. *et al.*, "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in *Hu*man colon tumors," *Proc. Natl. Acad. Sci. USA* 95:14717-14722 (1998).
    F. Pitti, R.M. *et al.*, "Genomic amplification of a decoy receptor for Fas ligand in lung and colon cancer," *Nature* 396:699-703 (1998).
    G. Bieche, I. *et al.*, "Novel approach to quantitative polymerase chain reaction using real-time detection: Application to the detection of gene amplification in breast cancer," *Int. J. Cancer* 78:661-666 (1998).

2. Declaration of Avi Ashkenazi, Ph.D. under 35 C.F.R. §1.132, with attached Exhibit A (Curriculum Vitae).

3. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis I).

4. Orntoft, T.F., et al., "Genome-wide Study of Gene Copy Numbers, Transcripts, and Protein Levels in Pairs of Non-Invasive and Invasive *Hu*man Transitional Cell Carcinomas," *Molecular & Cellular Proteomics* **1**:37-45 (2002).

5. Hyman, E., et al., "Impact of DNA Amplification on Gene Expression Patterns in Breast Cancer," *Cancer Research* **62**:6240-6245 (2002).

6. Pollack, J.R., et al., "Microarray Analysis Reveals a Major Direct Role of DNA Copy Number Alteration in the Transcriptional Program of *Hu*man Breast Tumors," *Proc. Natl. Acad. Sci. USA* **99**:12963-12968 (2002).

7. Hanna, J.S., et al., "HER-2/neu Breast Cancer Predictive Testing," Pathology Associates Medical Laboratories (1999).

8. Sen, S., "Aneuploidy and cancer," *Curr. Opin. Oncol.* **12**:82-88 (2000).

9. Pennica, D. et al., "WISP genes are members of the connective tissue growth factor family that are up-regulated in Wnt-1-transformed cells and aberrantly expressed in *Hu*man colon tumors," *Proc. Natl. Acad. Sci. USA* **95**:14717-14722 (1998).

10. Gygi, S. P. et al., "Correlation between protein and mRNA abundance in yeast," *Mol. Cell. Biol.* **19**:1720-1730 (1999).

11. Hu, Y. et al., "Analysis of genomic and proteomic data using advanced literature mining," *Journal of Proteome Research* **2**:405-412 (2003).

12. Declaration of Paul Polakis, Ph.D. under 35 C.F.R. §1.132 (Polakis II).

13. Alberts, B., *et al.,* Molecular Biology of the Cell (3rd ed. 1994) Cell 3rd at 453 Figure 9-2 of Cell 3rd Cell 3rd at 403.

14. Alberts, B., *et al.,* Molecular Biology of the Cell (4rd ed.) In Cell 4th, Figure 6-3 on page 302 Figure 6-90 on page 364 of Cell 4th Cell 4th at 364 Cell 4th at 379.

15. Futcher, B., *et al.,* Mol Cell Biol., - 19(11):7357-68 (1999).

16. Grenback, E., *et al.,* Regul Pept, - 117(2):127-39 (2004).

17. Lewin, B., Genes VI Genes VI at 847-848 (1997).

18. Meric, F., *et al.,* Molecular Cancer Therapeutics - 1:971-979 (2002).

19. Papotti, M., *et al.,* Virchows Arch. - 440(5):461-75 (2002).

20. Rudlowski, C., *et al.,* Am J. Clin Pathol. - 120(5):691-8 (2003).

21. Van Der Wilt, C.L., *et al.,* Eur J Cancer - 39(5):691-7 (2003).

22. Li *et al.*, 2006, Oncogene, 25: 2628-2635.

23. Nagaraja *et al.*, 2006, Oncogene 25: 2328-2338.

24. Waghray *et al.*, 2001, Proteomics, 1: 1327-1338.

25. Sagynaliev *et al.*, 2005, Proteomics, 5: 3066-3076.

Items 1-7 were submitted with Appellants' Response filed September 14, 2004, and acknowledged as having been considered by the Examiner in the Office Action mailed July 19, 2005.

Items 8-10 were made of record by the Examiner in the Office Action mailed May 20, 2004.

Item 11 was made of record by the Examiner in the Office Action mailed July 19, 2005.

Items 12-21 were submitted with Appellants' Preliminary Amendment filed August 3, 2006, and were considered by the Examiner as indicated in the Final Office Action mailed November 1, 2006.

Items 22-25 were made of record by the Examiner in the Final Office Action mailed November 1, 2006.

10. RELATED PROCEEDINGS APPENDIX

None.

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